



# Conditional Survival in Uveal Melanoma

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**Purpose:** To investigate conditional survival in patients with uveal melanoma in the United States.

**Design:** Cohort study.

**Participants:** Patients were identified using International Classification of Disease for Oncology, Third Edition, codes for both morphologic features (melanoma, 8720–8790) and site (retina, C69.2; choroid, C69.3; and ciliary body, C69.4) from 1975 through 2011 using the Surveillance, Epidemiology, and End Results (SEER) database SEER 18.

**Methods:** Observed metastasis-free survival (MFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Conditional metastasis-free survival (cMFS) and conditional overall survival were calculated based on the observed MFS and OS. Relative survival also was calculated using the actuarial method. Survival to 5 and 10 years after diagnosis were calculated, conditioned on various numbers of years already survived.

**Main Outcome Measures:** Conditional MFS, conditional OS, and conditional relative survival.

**Results:** A total of 6863 cases of uveal melanoma were identified. Median follow-up among survivors was 11 years. During follow-up, 3883 patients died of any cause, and of these, 2131 deaths were the result of metastatic uveal melanoma. The nonconditional 5-year MFS was 80%. After surviving 1, 2, 3, or 4 years after diagnosis, the 5-year cMFS estimates increased to 82%, 87%, 92%, and 96%, respectively. The nonconditional MFS at 10 years was estimated to be 69%. After having survived 5, 6, 7, 8, or 9 years after diagnosis, the 10-year cMFS estimates increased to 87%, 90%, 93%, 96%, and 98%, respectively. This result pattern was confirmed with estimates of relative survival.

**Conclusions:** Conditional survival estimates of uveal melanoma improve with time since primary diagnosis. Among patients who already have survived for at least 5 years, 10-year conditional survival rates are high. Conditional survival analysis can provide specific guidance for counselling patients. *Ophthalmology Retina* 2020;■:1–7 © 2020 by the American Academy of Ophthalmology

Uveal melanoma survival outcomes usually are reported as metastasis-free survival (MFS)<sup>1</sup> or all-cause overall survival (OS) derived by the Kaplan-Meier method.<sup>2</sup> The Kaplan-Meier method adjusts for the variable follow-up duration of each patient and the fact that some patients will still be alive (i.e., censored) at the time of analysis.<sup>1,3</sup> A rigorous method for ascertaining the presence of metastasis is essential to estimating MFS, and it is well known that hospital registries<sup>4,5</sup> and national databases can be inaccurate.<sup>6</sup> Additionally, except in carefully conducted studies such as the Collaborative Ocular Melanoma Study, which has its own system of validating metastasis,<sup>7</sup> the cause of death is not always known with certainty. Inaccuracies in outcome ascertainment become particularly relevant when analyzing long-term survival outcomes in uveal melanoma.<sup>8</sup> With a median age at diagnosis of 62 years,<sup>9</sup> it is not surprising that patients with uveal melanoma die of causes other than metastatic disease over the long term, and deaths resulting from metastatic uveal melanoma plateau at approximately 25 years after diagnosis.<sup>5,6,10</sup> (Singh AD, Zabor EC, Radivoyevitch T. Uveal melanoma: evidence of cure? Submitted 2020.) In a large United States population-based

cohort, other causes of death were more common than metastatic uveal melanoma. (Radivoyevitch T, Zabor EC, Singh AD. Uveal melanoma: long-term survival. Submitted 2020.)

As an alternative to MFS, relative survival (RS) methods can be used to estimate long-term survival without knowing the exact cause of death.<sup>11</sup> In RS approaches, survival probabilities observed in those with the cancer of interest (i.e., uveal melanoma) are divided by survival probabilities expected in age-, year-, and gender-matched healthy individuals from the same population. Thus, RS avoids use of cause of death and instead uses background mortalities.<sup>11,12</sup> Relative survival methods have been used to report long-term survival in uveal melanoma patients. (Radivoyevitch T, Zabor EC, Singh AD. Uveal melanoma: long-term survival. Submitted 2020.)<sup>13</sup>

Metastasis-free survival and RS in uveal melanoma are estimated from the time of diagnosis and therefore are static by design. That is, these survival estimates cannot be applied to the patient who already has survived a certain number of years since initial treatment. Patients who already have survived for some time often inquire about their chances of surviving additional years, a question that cannot

be answered using static estimators. Conditional survival is a dynamic estimate of the probability that a person will survive for an additional specified duration, conditioned on having already survived a certain number of years.<sup>14</sup> Conditional survival accounts for increasing survival probability with additional years survived.<sup>14,15</sup> Herein, we present estimates of conditional survival in uveal melanoma patients.

## Methods

### Data Selection

The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database file was accessed using SEER\*Stat software version 8.3.6.1 ([seer.cancer.gov/seerstat](http://seer.cancer.gov/seerstat)). Because data from the SEER registry are de-identified and publicly available, institutional review board approval was not needed. For inclusion of an institutional de-identified dataset, institutional review board approval was obtained. The study adhered to the tenets of the Declaration of Helsinki. No informed consent was obtained as data are de-identified and publicly available. Cases of ocular melanoma were identified using the International Classification of Disease for Oncology, Third Edition, codes for both morphologic features (melanoma, 8720–8790) and site (retina, C69.2; choroid, C69.3; and ciliary body, C69.4). As noted in previous reports derived from SEER data, “retinal melanoma” is a coding error accounting for approximately 1% of uveal melanoma cases.<sup>9</sup>

For analysis of MFS and OS, a case listing was extracted from the SEER 18 database, resulting in 10 676 cases diagnosed between 1975 and 2016.<sup>16</sup> After extraction from SEER\*Stat, additional exclusions were made. Patients were excluded if the uveal melanoma was not the first primary malignancy ( $n = 1527$ ), if cause of death was unknown or missing ( $n = 57$ ), and if survival months was either missing or listed as definitely or possibly being 0 days ( $n = 25$ ). Finally, patients diagnosed after 2011 were excluded to ensure adequate follow-up time for conditional survival analyses ( $n = 2204$ ). For analysis of RS, patients in the SEER 18 research database diagnosed between 2000 and 2016 were included, and those with survival data based only on death certificate or autopsy or who were alive with no survival time were excluded.<sup>17</sup> Patients were limited to those diagnosed before 2011 to ensure adequate follow-up time.

To consider stratification on important molecular prognostic factors (mutation status), published datasets of prognosticated patients from Cleveland Clinic,<sup>18,19</sup> the University of Iowa,<sup>19</sup> the Rotterdam Ocular Melanoma Study,<sup>20</sup> and the Liverpool Ocular Oncology Centre were pooled.<sup>21</sup> Patients were assessed according to subgroups with pathogenic *BAP1* mutation or *SF3B1* mutation and conditional MFS curves were produced, stratified by pathogenic mutation status.<sup>20,21</sup>

### Data Analysis

Observed survival estimates (the proportion of cancer patients surviving for a specified period) were calculated by the Kaplan-Meier method for either MFS or OS. Conditional survival estimates were calculated from the observed survival estimates. If  $S(t)$  represents the survival function at time  $t$ , then conditional survival is defined<sup>22</sup> as

$$S(y|x) = \frac{S(x+y)}{S(x)}$$

where  $y$  is the number of additional survival years of interest and  $x$  is the number of years a patient already has survived. For

example, to compute the conditional survival to 5 years for a patient who already has survived 3 years from diagnosis, the survival at  $2 + 3$  years,  $S(5)$ , is divided by the survival at 3 years,  $S(3)$ . We calculated both conditional MFS (cMFS) and conditional OS. Landmark analyses were used to obtain conditional survival curves for visualization purposes, where the landmark time was the number of years already survived since diagnosis. Statistical analyses were conducted using R software version 4.0.0 (R Core Development Team, Vienna, Austria) and the *condsurv* R package.<sup>23</sup> Age-standardized estimates of RS and conditional RS were calculated using the actuarial method and based on the Ederer II calculation<sup>24</sup> of expected survival according to the socioeconomic status, geography, race, and age of the United States population.

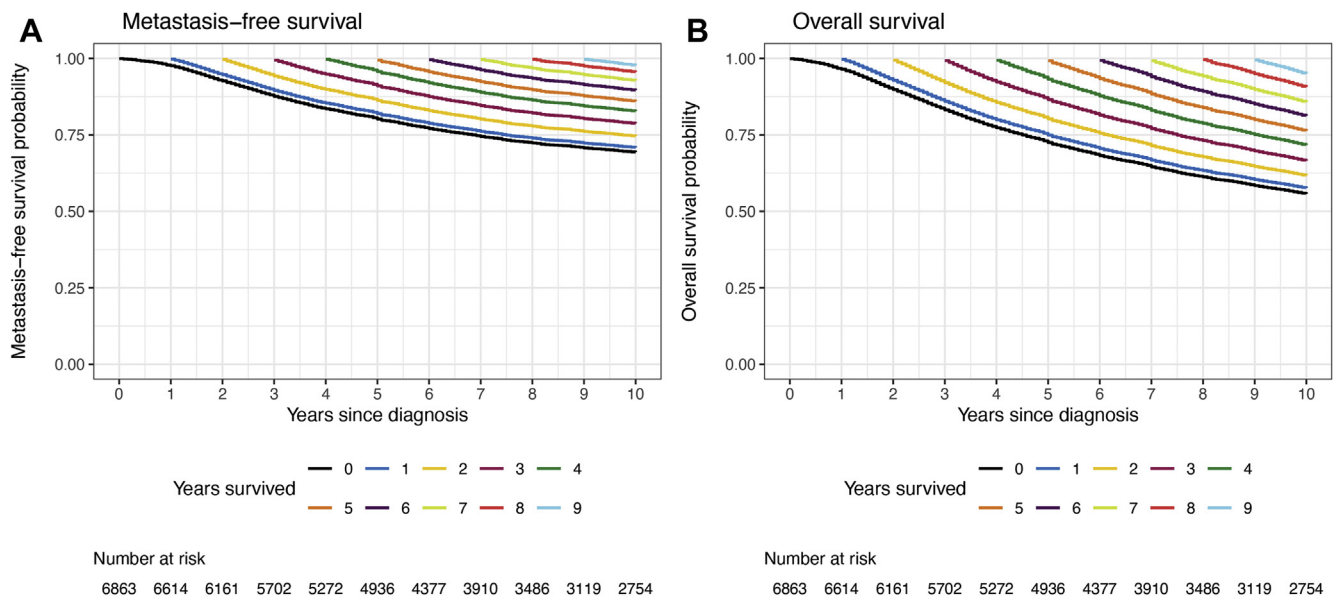
## Results

After exclusions, a total of 6863 uveal melanoma patients were available from SEER for analysis of MFS and OS. The median follow-up time among survivors was 11 years (range, 0–42 years). During follow-up, a total of 3883 patients died of any cause, and 2131 of these deaths were the result of uveal melanoma. We demonstrated that the MFS curves plateau beyond 25 years after diagnosis (Fig 1A). The plateau of the nonconditional curve was estimated to occur at just more than 50%, indicating that the cumulative proportion of patients dying by this time is approximately 50%. However, for patients who already have survived 10 years since diagnosis, this plateau occurred at approximately 75%, suggesting that only one quarter of these patients subsequently will die of the disease.

The nonconditional 5-year MFS was 80% (Table 1). After surviving 1, 2, 3, and 4 years after diagnosis, the 5-year cMFS estimates increased to 82%, 87%, 92%, and 96%, respectively. The nonconditional 10-year MFS was 69%. Among those who had survived 5, 6, 7, 8, and 9 years after diagnosis, estimates of 10-year cMFS increased to 87%, 90%, 93%, 96%, and 98%, respectively. However, OS did not improve as much over the long term (Fig 1B). Some gains were seen in the early years, such as an improvement in survival to 5 years from the nonconditional estimate of 73% to 87% after having survived for 3 years and an improvement in survival to 10 years from the nonconditional estimate of 56% to 86% after having survived for 7 years (Table 1).

A total of 4168 uveal melanoma patients from the SEER database were included in analysis of RS. The nonconditional 5-year RS was 81% (Table 2). After surviving 1, 2, 3, and 4 years after diagnosis, the 5-year conditional RS estimates increased to 82%, 86%, 91%, and 96%, respectively. The nonconditional 10-year RS was 70%. Among those who had survived 5, 6, 7, 8, and 9 years after diagnosis, estimates of 10-year conditional RS increased to 86%, 89%, 92%, 95%, and 98%, respectively (Fig 2).

A total of 788 prognosticated cases were available for analysis after combining data from 3 institutional databases. Median follow-up among survivors was 4 years (range, 0–25 years), and 259 patients were followed up for at least 5 years. During follow-up, 271 patients died of any cause, and of these deaths, 173 were the result of metastasis. Because of the limited follow-up in this cohort, we limited the analyses to evaluation of Kaplan-Meier plots. Of the multi-institutional prognosticated patients, 204 demonstrated a *BAP1* mutation and 60 demonstrated an *SF3B1* mutation.<sup>21</sup> (Singh AD, Zabor EC, Radivoyevitch T. Uveal melanoma: evidence of



**Figure 1.** Graphs showing Surveillance, Epidemiology, and End Results data: overall and conditional (A) metastasis-free and (B) overall survival curves.

cure? Submitted 2020.) For patients with *BAP1*-mutant uveal melanomas, a steep initial decline in MFS was found, reaching 50% at 5 years and improving to 90% if the patient survived 4 years since the diagnosis (Fig 3B). In contrast, for patients with *SF3B1*-mutant uveal melanomas, the MFS of 50% was evident after 10 years and was not impacted by the initial survival (Fig 3C).

## Discussion

After an early increase in the mortality rate after ocular therapy with enucleation,<sup>25</sup> episcleral plaque radiation therapy,<sup>26</sup> and proton beam radiation therapy,<sup>5,26</sup> mortality rates for uveal melanoma return toward baseline, rapidly

at first and then more slowly, becoming negligible approximately 25 years after ocular therapy. (Singh AD, Zabor EC, Radivoyevitch T. Uveal melanoma: evidence of cure? Submitted 2020.)

In the present analysis, we incorporated the concept of conditional survival to account for changing survival probabilities that increase with additional years survived.<sup>14,15</sup> To our knowledge, the estimates of conditional survival in uveal melanoma patients presented here have not been reported previously. Conditional survival is a dynamic measure of probability that a person will survive for an additional specified duration, conditioned on having already survived a certain number of years.<sup>14</sup> As a rule, conditional survival improves over time, so

Table 1. Estimates of Overall and Conditional Cancer-Specific Survival and Overall Survival

Years since Diagnosis	Metastasis-Free Survival	Overall Survival	No.*	No. of Metastasis-Free Survival Events	No. of Overall Survival Events	Conditional Metastasis-Free Survival	Conditional Overall Survival
5-Year Survival							
1	0.98 (0.97–0.98)	0.96 (0.96–0.97)	6614	1984	3660	0.82 (0.81–0.83)	0.75 (0.74–0.76)
2	0.93 (0.92–0.93)	0.90 (0.89–0.91)	6161	1656	3223	0.87 (0.86–0.87)	0.81 (0.80–0.82)
3	0.88 (0.87–0.88)	0.83 (0.82–0.84)	5702	1337	2775	0.92 (0.91–0.92)	0.87 (0.86–0.88)
4	0.84 (0.83–0.84)	0.77 (0.76–0.78)	5272	1062	2369	0.96 (0.95–0.96)	0.94 (0.93–0.94)
5	0.80 (0.79–0.81)	0.73 (0.71–0.74)	—	—	—	—	—
10-Year Survival							
5	0.80 (0.79–0.81)	0.72 (0.71–0.74)	4936	866	2048	0.87 (0.85–0.88)	0.77 (0.76–0.78)
6	0.77 (0.76–0.78)	0.68 (0.67–0.69)	4377	674	1759	0.90 (0.89–0.91)	0.82 (0.80–0.83)
7	0.74 (0.73–0.76)	0.65 (0.63–0.66)	3910	529	1533	0.93 (0.92–0.94)	0.86 (0.85–0.88)
8	0.72 (0.71–0.73)	0.61 (0.60–0.62)	3486	419	1326	0.96 (0.95–0.97)	0.91 (0.90–0.92)
9	0.71 (0.70–0.72)	0.58 (0.57–0.60)	3119	344	1171	0.98 (0.97–0.99)	0.95 (0.95–0.96)
10	0.69 (0.68–0.71)	0.56 (0.55–0.57)	—	—	—	—	—

Data are presented as the estimate (95% confidence interval). Columns of conditional survival are conditioned on the number of years since diagnosis on the given row.

\*Number of patients included in conditional survival calculations; — = N/A.

Table 2. Estimates of Overall and Conditional Relative Survival

Years since Diagnosis	Relative Survival	No.*	No. of Events	Conditional Relative Survival
				5-Year Survival
1	0.99 (0.98, 1.00)	4029	1718	0.82 (0.80, 0.84)
2	0.95 (0.93, 0.96)	3763	1468	0.86 (0.84, 0.88)
3	0.90 (0.88, 0.91)	3488	1204	0.91 (0.89, 0.92)
4	0.85 (0.83, 0.87)	3224	964	0.96 (0.95, 0.97)
5	0.81 (0.79, 0.83)	—	—	—
				10-Year Survival
5	0.81 (0.79, 0.83)	3045	775	0.86 (0.82, 0.88)
6	0.79 (0.76, 0.81)	2619	608	0.89 (0.86, 0.91)
7	0.76 (0.74, 0.78)	2241	477	0.92 (0.89, 0.94)
8	0.73 (0.71, 0.76)	1911	357	0.95 (0.92, 0.97)
9	0.72 (0.69, 0.74)	1601	268	0.98 (0.96, 0.99)
10	0.70 (0.67, 0.73)	—	—	—

Data are estimate (95% confidence interval). Columns of conditional survival are conditioned on the number of years since diagnosis on the given row.  
 \*Number of patients included in conditional survival calculations; — = N/A.

we see the improvement in both MFS and OS as we condition on an increasing number of years already survived (Fig 1). The nonconditional MFS at 10 years is estimated to be 69% at the time of diagnosis. After having survived 5 and 9 years since diagnosis, the 10-year cMFS increased to 87% and 98%, respectively. The RS of uveal melanoma patients at 10 years also improved from a baseline value of 70% to 86% and 98%

among those having survived 5 and 9 years since diagnosis, respectively (Table 2).

Prognostic factors that predict survival change with time because the survival itself changes with time.<sup>27</sup> In a recent study, Dogrusöz et al<sup>27</sup> used a landmark analysis approach to compare prognostic factors associated with survival at the time of enucleation and among those who survived for 5 years after enucleation. They found that only male

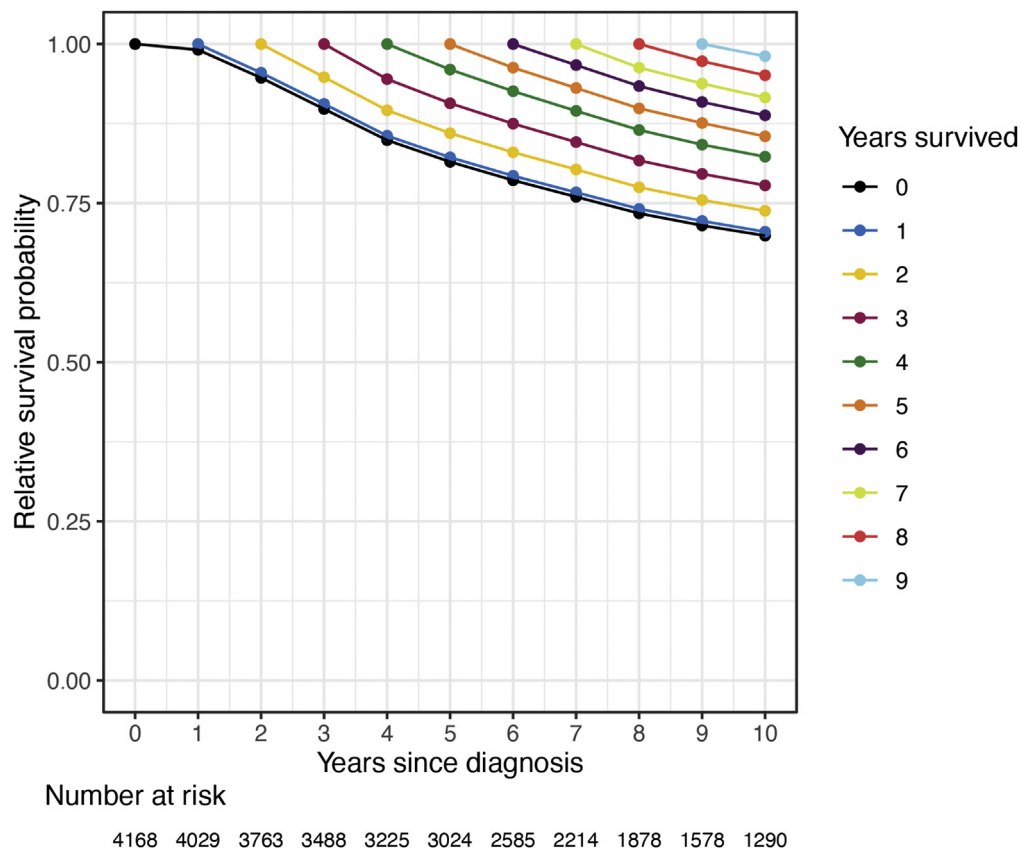
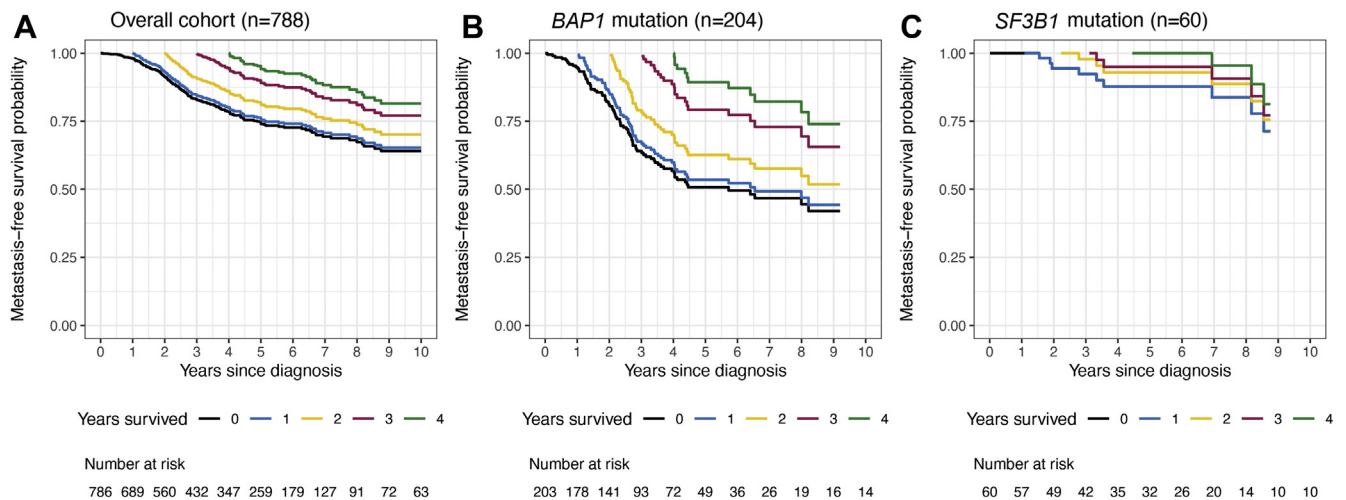


Figure 2. Graph showing Surveillance, Epidemiology, and End Results data: relative survival probabilities.





**Figure 3.** Graphs showing prognosticated patient data. Kaplan-Meier plots of (A) the overall cohort (n = 788), (B) the cohort with a *BAP1* mutation (n = 204) and (C) the cohort with an *SF3B1* mutation (n = 60).

gender and chromosome 8q gain remained associated significantly with survival among patients who had survived for 5 years. However, they did not report on estimates of conditional survival at various times as we have here. To our knowledge, the estimates of conditional survival in uveal melanoma patients presented herein have not been reported previously. These estimates are of interest to both clinicians and patients who have survived some years after a uveal melanoma diagnosis.

We used the SEER database, a national, population-based dataset<sup>16</sup> that readily meets some of the important prerequisites for conditional survival analyses, such as having a large number of patients (including uveal melanoma<sup>9</sup>) who have had long-term follow-up.<sup>28</sup> The SEER data are the source of summary statistics that are published annually as the national cancer report for all cancer-related statistics in the United States.<sup>29</sup> Even so, underreporting of metastatic deaths in the SEER dataset can be expected because the cause of death is determined from death certificates.<sup>30</sup> Moreover, the patients included in the SEER dataset are population based and not selected based on prognostication. Even tumor staging (American Joint Committee on Cancer AJCC seventh edition)<sup>31</sup> is available in SEER data starting only in 2010, insufficient for a robust long-term CS analysis by tumor size.

The conditional survival analysis can be applied easily to uveal melanoma patients prognosticated by size, molecular prognostic test results, or a combination of variables.<sup>32</sup> In the multi-institutional dataset available to us,<sup>20,21</sup> (Singh AD, Zabor EC, Radvovitch T. Uveal melanoma: evidence of cure? Submitted 2020.) the cMFS improved in *BAP1*-mutant uveal melanomas, but not in patients with *SF3B1*-mutant uveal melanomas, by the initial survival (Fig 3). With the median follow-up among survivors of 4 years (range, 0–25 years) and only a few patients remaining in the risk set by 10 years, interpretations should be limited to the earlier part of follow-up.

The results of this study should be considered only as a guide. The methods expounded herein can be applied to any

existing institutional data and can be customized as desired to make it clinically applicable, informative, and individualized to the patient. While counselling patients for systemic surveillance,<sup>33</sup> given the low risks of metastatic events beyond 15 years and the patient's advancing age, discontinuation of the systemic surveillance may be worthy of consideration, particularly in those without pathogenic somatic mutations.

This analysis has a number of limitations. The cause of death data available in the SEER database to estimate MFS is inherently biased, because cause of death is determined from death certificates, and thus may be erroneous. Additionally, use of MFS as an end point does not account for the competing event of death resulting from other causes. Over time, an increasing number of uveal melanoma patients will die of causes other than disease.<sup>6</sup> We partly accounted for this by comparing analyses of MFS with those using an RS approach<sup>13</sup> and found similar results. However, RS cannot fully overcome the bias introduced by imperfect cause of death attribution, so numbers here should be used with caution. Finally, despite the long follow-up for some patients, insufficient patients remained in the risk set beyond 10 years to estimate conditional survival confidently past this point and to assess long-term survival accurately.

In conclusion, conditional survival estimates of uveal melanoma improve with time since diagnosis. Among patients who already have survived for 5 or more years, 10-year conditional survival rates are high. Conditional survival analysis can provide specific guidance for counselling patients and their surveillance management.

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**HUMAN SUBJECTS:** Human subjects were included in this study. Because data from the Surveillance, Epidemiology, and End Results registry are de-identified and publicly available, institutional review board approval was not needed. For inclusion of an institutional de-identified dataset, institutional review board approval was obtained. All research adhered to the tenets of the Declaration of Helsinki. No informed consent was obtained as data are de-identified and publicly available.

No animal subjects were included in this study.

## Author Contributions:

Conception and design: Zabor, Radivoyevitch, Singh, Kilic

Analysis and interpretation: Zabor, Radivoyevitch, Singh, Kilic, de Klein, Kalirai, Coupland

Data collection: Zabor, Radivoyevitch, Kilic, de Klein, Kalirai, Coupland

Obtained funding: N/A

Overall responsibility: Zabor, Radivoyevitch, Singh, Kilic, de Klein, Kalirai, Coupland

## Abbreviations and Acronyms:

**cMFS** = conditional metastasis-free survival; **MFS** = metastasis-free survival; **OS** = overall survival; **RS** = relative survival; **SEER** = Surveillance, Epidemiology, and End Results.

## Keywords:

Conditional survival, Uveal melanoma.

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